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VOL. 23, SEC. B. MAY, 1945 NUMBER 3

A COLORIMETRIC METHOD FOR THE ESTIMATION OF REDUCING GROUPS IN MILK POWDERS[1]

BY R. A. CHAPMAN[2] AND W. D. McFARLANE[3]

Abstract

A method has been developed for the detection and estimation of certain reducing groups in milk powders. The method is based on the reduction of potassium ferricyanide at 70° C. and pH 5 and colorimetric estimation of ferric ferrocyanide. Titration with 2,6-dichlorophenolindophenol or potassium iodate failed to show any difference between fresh and stale milk powders. In contrast the ferricyanide test indicates much higher values in fresh powders than do the titration methods, and it also reveals a marked increase in samples that have developed stale, musty odours and flavours. Lactalbumin and casein show reducing activity that increases on heating. Of the amino acids tested, only tryptophane gives a positive reaction. It is concluded that the reducing groups are present in the protein molecule and become accessible on denaturation.

Introduction

Holm and Greenbank (14), Supplee (24), and Lea, Moran, and Smith (18) have correlated the development of stale, musty odours and flavours in milk powder with changes in the proteins. Gould and Sommer (7) report an increase in sulphydryl groups in milk held at 76° to 79° C. for a few minutes, and Gould (6) believes that a close correlation exists between cooked flavour in milk and the liberation of sulphydryl groups. Josephson and Doan (17) found that when milk, cream, or skim-milk was heated to a sufficiently high temperature, sulphydryl compounds were formed that were natural antioxidants and were responsible for inhibiting the development of tallowy or oxidized flavours. The presence of sulphydryl groups has also been suggested by Jack and Henderson (15) as the reason for the improved stability of milk powders produced from milk preheated to high temperatures.

It therefore appeared advisable to develop a method for the quantitative estimation of reducing groups in milk powders in order that the effect of these groups on the storage life of the product might be evaluated. The presence of sulphydryl groups has been detected by the nitroprusside test, but this colour reaction has not been applied quantitatively. Mirsky and Anson (19) have employed a method involving the reduction of cystine to cysteine by sulphydryl groups, followed by colorimetric estimation of the cysteine. These workers (20, 21) later suggested the use of iodoacetate, hydrogen peroxide, or potassium ferricyanide in the estimation of reducing groups, while Todrick and Walker (25) have measured the reduction of 2,6-dichlorophenolindophenol by a known amount of protein.

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[2] *Research Assistant in Chemistry.*

[3] *Professor of Chemistry.*

Porphyrindin has been used by Greenstein and his associates (4, 9, 10, 11) to titrate the reducing groups in a protein solution, but Anson (1) preferred to estimate sulphydryl compounds by the amount of tetrathionate or *p*-chloromercurobenzoate required to abolish the colour reaction with nitroprusside. The substituent sulphydryl groups of egg albumin have been determined by Guthrie and Allerton (12) employing the former's method for glutathione, and by Hellerman, Chinard, and Ramsdell (13) who used *o*-iodobenzoic acid for this purpose. Townley and Gould (26, 27, 28) have investigated the heat-labile sulphides in milk by aspirating with nitrogen during the heat treatment of the liquid and collecting the liberated sulphides in alkaline zinc acetate. The sulphides present were then determined by photometric measurements of the methylene blue produced on the addition of *p*-aminodimethylaniline and ferric chloride.

It appeared that the reduction of ferricyanide offered the best possibilities as the basis of a method for the estimation of reducing groups in milk powder. Preliminary tests indicated that stale powders had greater reducing power than fresh samples when allowed to react in alkaline solution with potassium ferricyanide. Experiments were therefore conducted to establish the optimum conditions for the ferricyanide test as applied to the estimation of reducing groups in milk powder.

Experimental

The Determination of Optimum Conditions

The method of Mirsky and Anson (21) as applied to the estimation of sulphydryl groups in egg albumin and serum globulin was investigated, and found unsatisfactory. After precipitation with tungstic acid, a considerable portion of the ferrocyanide was adsorbed on the flocculent precipitate of the milk protein. Trichloroacetic acid was more satisfactory, as the filtrate gave a very definite dark blue colour, indicating that the ferrocyanide was not adsorbed.

It was found that hydrogen ion concentration had a very marked effect on the activity of the reducing groups. Early experiments, conducted at room temperature, indicated that sulphydryl groups did not show reducing properties until the solution was made alkaline. The activity of the reducing groups increased markedly up to pH 11 but the difference between fresh and stale powders was small in relation to the total values. Further experiments, however, indicated that if the solutions were heated to 70° C. for 20 min. the sulphydryl groups became reactive at a much higher hydrogen ion concentration. The effect of hydrogen ion concentration is shown in Fig. 1. It is evident that the activity of the reducing groups in the stale powder increased with a decrease in hydrogen ion concentration, but the values obtained with the fresh sample remained comparatively constant until above pH 5. Therefore, pH 5 would give the most satisfactory results; so, in subsequent experiments the solution was adjusted by the addition of 5 ml. of potassium-acid-phthalate sodium-hydroxide buffer. The colour intensity reached a maximum at concentrations of potassium ferricyanide above 0.25%. Five millilitres of a 1% solution was employed in the test.

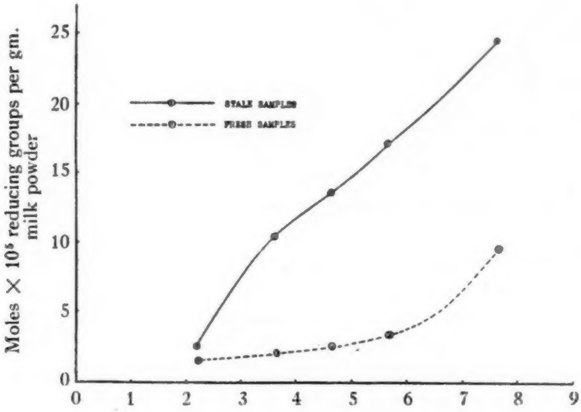

FIG. 1. *Effect of hydrogen ion concentration on the formation of reducing groups in solutions of fresh and stale milk powders heated at 70° C. for 20 min.*

An aqueous solution of ferric sulphate containing gum ghatti was used by Mirsky and Anson (21) to develop the Prussian blue. However, we found that a freshly prepared ferric chloride solution was satisfactory. The ferri-ferrocyanide tended to precipitate on standing several hours, but no difficulty was encountered during the period required for the test.

The reaction between denatured milk protein and potassium ferricyanide was relatively slow at pH 5. Other investigators (21, 25) have also observed that the protein still reduced potassium ferricyanide after 12 to 24 hr. A reaction time of 20 min. was chosen and the results are, therefore, comparative rather than absolute.

The effect of the time of reaction on the intensity of the colour is shown in Fig. 2.

DESCRIPTION OF THE FERRICYANIDE METHOD

As a result of the foregoing experiments, the following method was adopted:–

A 100 mg. sample of milk powder was weighed into a test-tube (22 by 150 mm.), 5 ml. of distilled water at 70° C. was added and the solution thoroughly mixed. Then 5 ml. of potassium-acid-phthalate–sodium-hydroxide buffer pH 5, and 5 ml. of a 1% solution of potassium ferricyanide were added. A blank, which contained all the reagents except the milk powder, was pre-

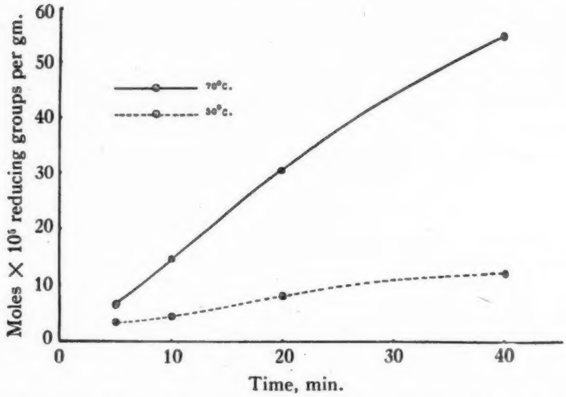

FIG. 2. *Effect of time of reaction on the intensity of the colour.*

pared. The tubes were placed in a water-bath at 70° C. for exactly 20 min. and then transferred to a beaker of ice-water and allowed to cool to 25° C. Five millilitres of a 10% solution of trichloracetic acid was added and after filtering through a No. 40 Whatman filter paper, 5 ml. of the filtrate was transferred to a colorimeter tube. Five millilitres of distilled water and 1 ml. of freshly prepared 0.1% solution of ferric chloride were added and the tubes shaken. The tubes were allowed to stand for 10 min. and then the intensity of the colour was read in an Evelyn colorimeter (660 mμ filter), adjusted to read 100% transmission with the reagent blank.

A calibration curve was prepared, glutathione being used, although cysteine was equally satisfactory. Glutathione rapidly reduced potassium ferricyanide under the conditions of the test and a stable colour of maximum intensity was obtained after heating for a few minutes. The glutathione solution must be prepared in freshly boiled, distilled water saturated with carbon dioxide to prevent autoxidation. The calibration curve (Fig. 3) was prepared by subjecting glutathione solutions of varying concentrations to the entire procedure and expressing the galvanometer readings as moles × 10^5 of glutathione, or as reducing groups, since glutathione has one SH group per mole. Owing to the fact that the ferric ferrocyanide was not in true solution, but was present as a highly dispersed suspensoid sol, the values did not follow Beer's law. Thus it was necessary to refer to the calibration curve in all calculations with milk powder.

STUDIES ON THE APPLICATION OF THE TEST AND FACTORS INFLUENCING THE RESULTS

I. *Heated Milks*

A number of workers (3, 6, 7, 8, 16, 17) have discussed the effect of heating milk in regard to off-flavours and the production of reducing substances. It appeared of interest, therefore, to apply the ferricyanide procedure to the

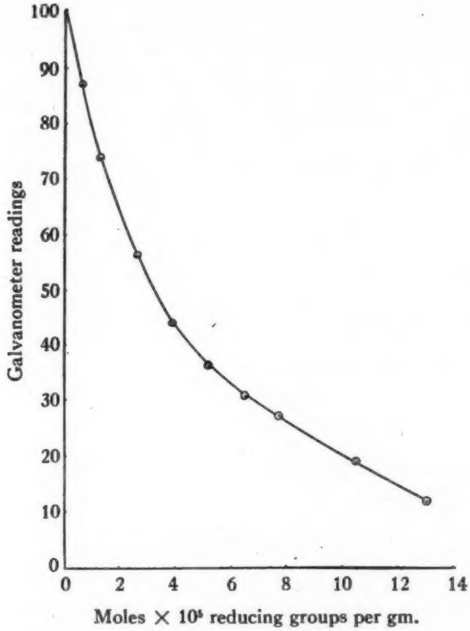

FIG. 3. *Calibration curve of ferricyanide test with glutathione.*

determination of the reducing power of raw milk heated to various temperatures and immediately cooled. Samples of milk powders were also included in the test. The values given in Table I indicate that there is an increase in reducing groups on heating. The effect of heating during processing is also very evident as the roller-process whole milk powders have a much higher content of reducing groups than spray-dried powders. The milk powder prepared by high-vacuum drying in the frozen state gave a value almost identical with that of the fresh milk.

The nitroprusside test of Gould and Sommer (7) was applied to all the samples included in Table I. Milk heated to 85° C. and 100° C. gave faint but definitely positive reactions, but all other samples were negative. The positive tests with liquid milk might have been due to volatile sulphides (26) and since the test was negative with milk powders, these sulphides could have been volatilized during drying.

II. *Amino Acids and Proteins*

Mirsky and Anson (21) believed that sulphydryl groups in the protein molecule were largely responsible for the reduction of potassium ferricyanide, although other groups, probably in tyrosine and tryptophane, also reduced this reagent. The cystine content of milk powder has been reported as 0.4% by Block and Bolling (2, p. 3) but the observed values for milk powder

TABLE I

THE EFFECT OF HEATING MILK AND MILK POWDERS IN RELATION TO REDUCING GROUPS

Sample and treatment	Reducing groups*
Raw milk	2.16 2.28
Raw milk heated to 63° C.	2.08 2.22
Raw milk heated to 85° C.	2.82 2.89
Raw milk heated to 100° C.	4.40 4.56
Raw milk evaporated to dryness at 100° C.	27.70 26.90
Spray-dried skim-milk powder heated to 204° C.	32.80 32.20
Spray-dried whole milk powder—fresh	
Sample A	4.20
Sample B	3.95
Roller-process whole milk powder—fresh	
Sample A	27.50
Sample B	25.80
Milk powder—prepared by drying in the frozen state	2.30

* *Moles × 10^5 reducing groups per gram of milk powder. The liquid milk was assumed to contain 12.5% of total solids. To compare skim-milk with whole milk powder the value for the former is calculated as if the skim-milk contained 27% fat. Before heating, the skim-milk powder gave a value similar to that of fresh spray-dried whole milk powder.*

are much higher than can be attributed to this source. It is thus apparent that other groups in the protein molecule or certain non-protein substances in milk powder must be involved in the reduction. The reducing power of a number of amino acids was therefore determined by the ferricyanide method, with the results shown in Table II. Glutathione and glycyl-glycine have been included for comparison. Tryptophane appears to be the only substance of those tested that exhibits any appreciable reducing power.

TABLE II

REDUCTION OF FERRICYANIDE BY AMINO ACIDS

Substance	Galvanometer reading	Substance	Galvanometer reading
Tryptophane	95.0	Serine	98.0
Tyrosine	100.0	Cystine	100.0
Histidine	99.25	Glycyl-glycine	99.5
Methionine	100.0	Glutathione	61.0
Hydroxyproline	98.0		

Determinations were also conducted on samples of casein, lactose, and lactalbumin. Two samples of casein were employed, a fresh sample prepared by the method of Moir (22) and purified according to that of Van Slyke and Baker (29), and an old sample produced in 1913 by Kahlbaum, Germany. The sample of lactalbumin was six years old. A fresh spray-process milk powder was also included in the test, and a portion of each sample was heated to 100° C. for 16 hr. The results are given in Table III.

TABLE III

REDUCING POWER OF LACTOSE, LACTALBUMIN, AND CASEIN

(Moles × 10^6 reducing groups per gm.)

Material	Unheated	Heated
Lactose	0.30	0.50
Lactalbumin—old sample	7.40	19.0
Casein—fresh sample	1.55	2.45
Casein—old sample	8.45	11.20
Milk powder	4.40	23.80

It is evident that lactalbumin and casein act as reducing substances. The effect of storage is clearly shown in the case of the casein prepared in 1913, which has a very much higher content of reducing groups than the fresh sample. Heating also increases the reducing power of the proteins in a manner analogous to the increase in the reducing groups in milk powder.

III. *Estimation of Reducing Groups by Titration with 2,6-Dichlorophenolindophenol or Potassium Iodate*

Gould (5) has employed 2,6-dichlorophenolindophenol and potassium iodate in a study of the reducing systems in milk. It appeared of value to determine the effect of storage conditions on the results obtained by these methods. A series of milk powders was tested, four of which had been allowed to stand open to the air for several months, while identical samples were held in sealed tins. The results, calculated as glutathione and ascorbic acid, are given in Table IV.

Notwithstanding the fact that the samples exposed to the atmosphere had developed strong, stale, musty odours and flavours it is evident that the reducing power of these milk powders was no higher than that of the sealed powders as measured by 2,6-dichlorophenolindophenol and potassium iodate. However, the ferricyanide method revealed that the reducing power of the milk powders open to the air was very much higher. In addition, the values obtained with the sealed samples were considerably larger than those given by the other methods. It would appear from these results that the potassium ferricyanide method is measuring reduction of an entirely different type.

In an effort to trace the source of the reducing groups in the milk powder, an attempt was made to separate the casein from the albumin and globulin

TABLE IV

A COMPARISON OF THE REDUCING POWER OF MILK POWDERS STORED IN OPEN AND CLOSED TINS

Sample	2,6-Dichlorophenolindophenol titration		Iodate titration		Ferricyanide colorimetry	
	A	*B*	*A*	*B*	*A*	*B*
A. Open tins						
No. 495218	0.0947	0.0273	0.184	0.0528	67.8	19.4
No. 495418	0.0874	0.0252	—	—	63.6	18.2
No. 495618	0.0916	0.0264	0.184	0.0528	55.4	15.9
No. 495818	0.0947	0.0273	—	—	69.7	20.0
B. Sealed tins						
No. 495218	0.0874	0.0252	0.295	0.0845	10.9	3.12
No. 495418	0.0855	0.0246	—	—	11.2	3.20
No. 495618	0.0916	0.0264	0.276	0.0792	9.8	2.82
No. 495818	0.0978	0.0282	—	—	13.5	3.97

A. Calculated as glutathione, mgm. per gm.
B. Calculated as ascorbic acid, mgm. per gm.

fractions. The method of Rowland (23) as outlined for liquid milk was applied to the reconstituted milk. The results indicated that approximately two-thirds of the reducing power was located in the casein fraction and one-third in the albumin and globulin fractions.

Discussion of the Method

The ferricyanide test indicates that reducing groups are present in milk and milk powders. The amount of reducing substances in milk powder was increased by exposure to the atmosphere, and it was noted that the increase in reducing power paralleled the development of stale, musty flavours and odours, and a marked decrease in the solubility of the powders. Lea, Moran, and Smith (18) believe that this type of deterioration is associated with the protein fraction of milk and our results appear to verify this conclusion.

Titration with potassium iodate and 2,6-dichlorophenolindophenol failed to reveal an increase in reducing groups in stale milk powders but the ferricyanide test indicated much higher values in fresh powders, and a marked increase in samples that had developed stale, musty odours and flavours. It has been shown that, at pH 6 to 8 (Fig. 1), there was a proportional increase in reducing groups in both powders, but when heated at pH 5 the fresh powders showed little reducing activity as compared to the stale powders. This effect is in accordance with the findings of Mirsky and Anson (21), that denatured protein is able to reduce the reagent in a more acid medium than native protein. Therefore, it would seem justifiable to conclude that the reducing groups are present in the protein molecule and become accessible on denaturation.

It should be emphasized that since the reduction was not allowed to go to completion, the measurements of reducing groups in milk powders are relative rather than absolute. A later paper, reporting on storage tests with whole milk powders, will present further results with the ferricyanide method in regard to the effect of reducing groups on keeping quality.

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SOME DERIVATIVES OF VICINAL TRIALKOXY-BENZENE[1]

BY RICHARD H. F. MANSKE[2], A. E. LEDINGHAM[3], AND H. L. HOLMES[4]

Abstract

During the course of some preliminary work leading to the synthesis of possible degradation products of capaurine a number of derivatives of vicinal trialkoxy-benzene were prepared. Those found to have a direct relation to the structure of the alkaloid have already been described. The present manuscript details the preparation of a number of such derivatives that did not prove to be germane to the main problem.

Although vicinal trialkoxy derivatives are widely distributed in nature, only three types of alkaloids are known to contain such groupings. In narcotine two of the oxygens are in combination with a methylene group, the third occurring as methoxyl. In colchicine there are three methoxyl groups and in capaurine (9) there are two vicinal methoxyls and a free hydroxyl. While elucidating the structure of capaurine a number of derivatives of pyrogallol and of gallic acid were prepared in the hope that 3-ethoxy-4,5-dimethoxy- and 4-ethoxy-3,5-dimethoxy-phthalic acids could be conveniently prepared. A synthesis of the former has already been described (9) but it has been obtained in small yield by another route. Ring closures of β-(2-ethoxy-3,4-dimethoxyphenyl)-propionic acid yielded a trialkoxy-α-hydrindone, which, on oxidation with aqueous permanganate, yielded the desired acid. Attempts to condense 2,3,4-trimethoxy-benzoic acid or the corresponding 2-ethoxy-derivative or their methyl esters with formaldehyde and hydrochloric acid or with chloral in sulphuric acid, failed to yield any condensation products whatever. This is an unexpected observation because 2,3-dimethoxy-benzoic (4, 10) and 3,4-dimethoxy-benzoic acids (3) condense readily with one or other of the specified reagents.

4-Ethoxy-3,5-dimethoxy-phthalic acid was readily obtained by oxidizing the corresponding phthalide. The latter was obtained along with its chloromethyl derivative by condensing syringic acid ethyl ether with formaldehyde and hydrochloric acid (7). The acid was characterized as the anhydride, the N-methylimide, and the N-ethylimide. The chloromethylphthalide was reduced to 5-ethoxy-4,6-dimethoxy-3-methylphthalide. The chloromethylphthalide obtained from 3,4,5-trimethoxy-benzoic acid (7) was also reduced to the 3-methylphthalide.

By the application of known reactions 2-hydroxy-3,4-dimethoxy- and 4-hydroxy-3,5-dimethoxy-benzaldehydes have been prepared. They were

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Contribution from the Research Laboratory, Dominion Rubber Company Limited, Guelph, Ontario.

[2] *Director of Research, Research Laboratory, Dominion Rubber Company Limited, Guelph, Ontario.*

[3] *Chemist, Research Laboratory, Dominion Rubber Company Limited, Guelph, Ontario.*

[4] *Associate Professor of Chemistry, University of Saskatchewan, Saskatoon, Sask.*

converted to their ethyl ethers, which were also obtained by the Rosenmund reduction of the corresponding acid chlorides.

Prior to the proof of the structure of capaurine there was the possibility that oxidation of its methyl ether would yield 5,6,7-trimethoxy-1-keto-1,2,3,4-tetrahydro-isoquinoline. This substance was prepared by heating β-(2,3,4-trimethoxyphenyl)-ethyl isocyanate with phosphoryl chloride in xylene. Intermediates and derivatives in this synthesis as well as a miscellany of new compounds are described in the experimental section.

Experimental

2-Hydroxy-3,4-dimethoxy-benzaldehyde

During the preparation of a large lot of pyrogallol trimethyl ether there was isolated a phenolic fraction whose methoxyl content indicated that it consisted substantially of 2,3-dimethoxy-phenol. 2,6-Dimethoxy-phenol could not be crystallized from the material when chilled. By treating it with zinc cyanide and hydrogen chloride in ether (1) the aldehyde group was introduced. There was obtained a 20% yield of purified aldehyde, which, when recrystallized twice from ether, melted at 74° C.* Calc. for $C_9H_{10}O_4$: C, 59.34; H, 5.49%. Found: C, 59.04, 59.24; H, 5.41, 5.43%.

An application of the Duff aldehyde synthesis (2) to the above-mentioned phenol gave the same aldehyde in about 20% yield. There was obtained a much less soluble by-product, which, when recrystallized several times from methanol–ether, melted at 142° C. and gave an intense blue colour with alcoholic ferric chloride. Analyses indicate that it is the dialdehyde of a pyrogallol monomethyl ether. It is not likely that the conditions of the synthesis are sufficiently drastic to eliminate a methoxyl group, and it is therefore probable that a small amount of pyrogallol monomethyl ether was present in the dimethyl ether. Calc. for $C_9H_8O_5$: C, 55.10; H, 4.08, OMe, 15.82%. Found: C, 55.14, 55.16; H, 4.29, 4.31; OMe, 15.49%.

2-Ethoxy-3,4-dimethoxy-benzaldehyde

The ethylation of 2-hydroxy-3,4-dimethoxy-benzaldehyde was carried out with diethyl sulphate and aqueous sodium hydroxide containing a little ethanol. Large excesses of reagents were necessary to bring about the alkylation of the sterically hindered hydroxyl, the reaction being continued until further addition of alkali failed to produce a precipitate of the sparingly soluble yellow sodium salt. The washed ether extract of the aldehyde was evaporated and the residue distilled *in vacuo*,—b.p. 165 to 170° C. (14 mm.). The aldehyde failed to crystallize. The *oxime* was recrystallized from hexane, and it then consisted of long stout needles melting at 70° C. Calc. for $C_{11}H_{15}O_4N$: N, 6.22%. Found: N, 6.15%.

A small portion of the aldehyde was oxidized to the corresponding acid, which, when recrystallized from hot water, melted sharply at 78° C. either alone or in admixture with a synthetic specimen of 2-ethoxy-3,4-dimethoxy-benzoic acid (*vide infra*).

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* *All melting points are corrected.*

Conversely, the aldehyde was prepared from 2-ethoxy-3,4-dimethoxy-benzoic acid via the acid chloride and Rosenmund reduction. A mixture of the acid (4.7 gm.) and phosphorus pentachloride (4.4 gm.) was gently warmed to complete the reaction and the mixture distilled *in vacuo*. There was obtained 4.5 gm. of product,—b.p. 178 to 179° C. (14 mm.); this was dissolved in dry toluene (60 cc.), and treated with barium-sulphate–palladium catalyst (1.0 gm.), and the stirred and boiling mixture treated with a stream of dry hydrogen. In 110 min. 85% of the theoretical amount of hydrogen chloride had been eliminated. The warm filtered toluene solution was shaken with aqueous sodium bicarbonate, the solvent removed, and the residue distilled *in vacuo*. There was obtained 2.8 gm. (72% of theory) of 2-ethoxy-3,4-dimethoxy-benzaldehyde boiling at 167 to 169° C. (14 mm.).

2-Ethoxy-3,4-dimethoxy-cinnamic Acid

A mixture of 2-ethoxy-3,4-dimethoxy-benzaldehyde (2.7 gm.), malonic acid (2.7 gm.), and pyridine (5.0 gm.) containing one drop of piperidine was heated on the steam-bath for two hours and then brought to gentle boiling over a free flame. It was then poured into a mixture of ice and dilute hydrochloric acid, and the crystals were filtered off, washed, and dried. There was obtained 2.6 gm. of 2-ethoxy-3,4-dimethoxy-cinnamic acid (m.p. 173 to 174° C.), which, when recrystallized from boiling water, melted at 178° C. and consisted of almost colourless needles. Calc. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39%. Found: C, 61.65, 61.49; H, 6.39, 6.62%.

β-(2-Ethoxy-3,4-dimethoxyphenyl)-propionic Acid

A suspension of the corresponding cinnamic acid (2.6 gm.) in water was treated with sodium amalgam until the alkaline solution failed to reduce a cold solution of permanganate instantly. Acidification of the aqueous solution yielded the *propionic* acid (2.3 gm.), which melted at 72° C. and when recrystallized thrice from hexane, it consisted of stout prisms melting sharply at 74° C. Calc. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.13%. Found: C, 61.59, 61.62; H, 7.13, 7.08%.

3-Ethoxy-4,5-dimethoxy-phthalic Anhydride

The above propionic acid was converted into 4-ethoxy-5,6-dimethoxy-hydrind-1-one by Perkin and Robinson's procedure (11). The crude hydrindone, which did not crystallize, was suspended in water and treated with successive portions of potassium permanganate until the reagent was no longer consumed. The heated solution was then treated with calcium chloride and ammonium chloride, filtered, acidified, and exhausted with ether. The residue from the ether extract was twice sublimed *in vacuo* and twice recrystallized from dry-ether–hexane. The 3-ethoxy-4,5-dimethoxy-phthalic anhydride thus obtained consisted of colourless fine needles melting at 108° C. either alone or in admixture with an authentic specimen (9).

2-Ethoxy-3,4-dimethoxy-benzoic Acid

The ethylation of 2-hydroxy-3,4-dimethoxy benzoic acid (6) with excess diethyl sulphate and alkali gave a quantitative yield of the *ethoxy-acid.* It crystallized from hot water in colourless needles melting at 79° C. Calc. for $C_{11}H_{14}O_5$: C, 58.41; H, 6.20%. Found: C, 58.45, 58.31; H, 6.51, 6.40%.

5,6,7-Trimethoxy-1-keto-1,2,3,4-tetrahydro-isoquinoline

The synthesis of the required intermediates was carried out by the procedure of Slotta and Heller (12). The yields were the following,—2,3,4-trimethoxybenzoyl chloride (b.p. 173 to 174° C. (13 mm.)) (92%); 2,3,4-trimethoxybenzaldehyde (b.p. 160 to 162° (10 mm.)) (70%); 2,3,4-trimethoxy-cinnamic acid (90%); and β-(2,3,4-trimethoxyphenyl)-propionic acid (89%). The last was converted into its methyl ester (b.p. 148 to 149° (2 mm.)) in 90% yield.

A mixture of the above-mentioned methyl ester (29.7 gm.) and hydrazine hydrate (12.0 gm.) was heated on the steam-bath for six hours. The cooled mixture, which solidified, was dissolved in water and treated at 0° C. with hydrochloric acid and aqueous sodium nitrite. The separated oily *azide* was extracted with benzene and the washed benzene solution evaporated at room temperature until all the water had been removed. The residual solution was then gently warmed to decompose the azide with the formation of the *isocyanate* and the liberation of nitrogen. Complete removal of the benzene, finally *in vacuo,* yielded 26.0 gm. of a pale wine coloured oil.

In order to effect ring closure, the isocyanate (10.0 gm.) in xylene (20 cc.) was heated under reflux with phosphorus oxychloride (10.0 gm.) and phosphorus pentoxide (0.3 gm.) for 75 min. The xylene and excess phosphorus oxychloride were removed *in vacuo.* The residue was treated with 150 cc. of dilute hydrochloric acid, cooled, filtered and exhausted with ether. The aqueous solution was then basified with an excess of sodium carbonate and extracted with several portions of chloroform. The residue from the chloroform extract was distilled *in vacuo.* The first fraction (b.p. 160 to 180° C. (1 mm.)) proved to consist largely of β-(2,3,4-trimethoxyphenyl)-ethylamine (3.3 gm.). The second fraction (b.p. 200 to 210° (1 mm.)) (0.4 gm.) solidified completely. It was recrystallized twice from dry ether. The isoquinolone as thus obtained consisted of rectangular prisms melting sharply at 124° C. Calc. for $C_{12}H_{15}O_4N$: C, 60.75; H, 6.37; N, 5.90%. Found: C, 60.71; H, 6.49; N, 5.71%.

A small portion was oxidized in aqueous solution (readily soluble in water) with potassium permanganate. The acid, isolated in the usual way, was sublimed *in vacuo,* and the resulting anhydride converted into the N-ethylimide which was sublimed *in vacuo* (160° (1 mm.)) and recrystallized from hot water. The 3,4,5-trimethoxy-N-ethylphthalimide thus obtained melted at 92 to 93° C. either alone or in admixture with an authentic specimen.

β-(2,3,4-Trimethoxyphenyl)N-ethylphthalimide

N-carbomethoxy-β-(2,3,4-trimethoxyphenyl)-ethylamine was prepared by heating the corresponding isocyanate (*vide supra*) with twice its weight of methanol for several hours. The methyl urethane was distilled *in vacuo* (b.p. 161 to 162° (1 mm.)) and obtained as a colourless oil (73% yield) that could not be crystallized. It was heated with an equal weight of phthalic anhydride (8) at 240° C. for one-half hour. The cooled melt was dissolved in methanol, much ether was added, and the mixture shaken repeatedly with dilute alkali. The residue from the washed ether solution crystallized when triturated with hexane. The washed solid then crystallized from methanol in flat rectangular plates melting at 110° C. Calc. for $C_{19}H_{19}O_5N$; N, 4.10%. Found: N, 4.01%.

3,5-Dimethoxy-4-hydroxy-benzaldehyde

Following the procedure of Duff (2), a solution of boric acid (35 gm.) in glycerol (150 gm.), which had been previously dehydrated by gradually heating to 170° C., was treated at this temperature with hexamethylenetetramine (25 gm.). The temperature fell to about 160° C. There was added almost immediately pyrogallol-1,3-dimethyl ether (25 gm.) and the mixture maintained at 150 to 155° C. for 15 min., cooled to 110° C. and diluted with a solution of sulphuric acid (30 cc.) in water (100 cc.). The cooled solution was then extracted with ether and the solvent removed from the washed extract. The residue was purified by distillation in a high vacuum and a portion recrystallized from methanol–water. The purified product was obtained in almost colourless needles melting at 114° C. Graebe and Martz (5) record m.p. 113° C.; yield 7 to 8 gm.

A portion of the aldehyde was ethylated with diethyl sulphate and alkali. The resulting oil was not obtained in a crystalline condition. The *oxime* was recrystallized from benzene–hexane and consisted of stout needles melting at 91° C. Calc. for $C_{11}H_{15}O_4N$; N, 6.22%. Found: 6.20%.

A portion of the ethyl ether was oxidized to syringic acid O-ethyl ether, which melted either alone or in admixture with an authentic specimen at 124° C.

4,6-Dimethoxy-5-ethoxy-phthalide

When the procedure of King and King (7) for the synthesis of the corresponding trimethoxy-phthalide was applied to syringic acid O-ethyl ether the above-named compound was obtained in good yield. It was recrystallized from dilute methanol and it then consisted of fine colourless needles melting at 92° C. The yield was virtually quantitative. Calc. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.88%. Found: C, 60.67, 60.85; H, 6.07, 5.93%.

4-Ethoxy-3,5-dimethoxy-phthalic Anhydride

The above-mentioned phthalide was dissolved in an excess of aqueous sodium hydroxide, and the cooled solution was saturated with carbon dioxide, and treated at room temperature with permanganate until no more reagent was consumed. The solution was treated with excess ammonium chloride and calcium chloride, filtered, and the acidified filtrate exhausted with ether. The residue from the ether extract was sublimed *in vacuo* and recrystallized from dry-ether–hexane. The anhydride then consisted of fine colourless needles melting sharply at 117° C. Calc. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.76%. Found: C, 57.32; H, 4.70%.

The N-methylimide was sublimed *in vacuo* and then recrystallized from ether. It consisted of fine needles melting at 124° C. Calc. for $C_{13}H_{15}O_5N$: N, 5.28%. Found: N, 5.22, 5.38%.

The N-ethylimide, similarly prepared and recrystallized from ether–hexane, consisted of stout prisms melting at 90° C. Calc. for $C_{14}H_{17}O_5N$: N, 5.02%. Found: N, 5.02, 5.16%.

2-Methyl-3,4,5-trimethoxy-phthalide

A solution of 2-chloromethyl-3,4,5-trimethoxy-phthalide (7) (8 gm.) in 95% ethanol (100 cc.) was heated under reflux with zinc dust (10 gm.), hydrochloric acid in small amounts being added at intervals until the zinc had dissolved. The ethanol was then distilled and the mixture extracted with ether. The residue from the washed ether solution crystallized from methanol in brilliant colourless needles, melting at 88° C. The compound was obtained in quantitative yield and was free of halogen. Calc. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.88%. Found: C, 60.62, 60.81; H, 6.13, 6.05%.

2-Methyl-4-ethoxy-3,5-dimethoxy-phthalide

The intermediate 2-chloromethyl-compound was prepared from syringic acid O-ethyl ether by the procedure of King and King (7). When recrystallized from methanol it consisted of colourless fine prisms melting at 84° C. The yield was virtually quantitative. Calc. for $C_{13}H_{15}O_5Cl$: C, 54.45; H, 5.24%. Found: C, 54.48, 54.76; H, 5.27, 5.37%.

The reduction of this chloromethyl-compound by the procedure detailed above yielded the halogen-free *2-methyl-4-ethoxy-3,5-dimethoxy-phthalide* in stout prisms melting at 82° C. when recrystallized from hexane or from a large volume of water containing several per cent of methanol. Calc. for $C_{13}H_{16}O_5$; C, 61.90; H, 6.35%. Found: C, 62.16, 62.13; H, 6.43, 6.37%.

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PREPARATION OF POLY(CHLOROMETHYL)BENZENES[1]

By Marshall Kulka[2]

Abstract

The chloromethylation of benzyl chloride under optimum conditions of solvent, condensing agent, and temperature resulted in a mixture from which *p*-di(chloromethyl)benzene (42%), *o*-di(chloromethyl)benzene (13%), *m*-di(chloromethyl)-benzene (3%), and di(*p*-chloromethylphenyl)methane (1%) were separated. Two new compounds, namely, 1,2,4-tri(chloromethyl)benzene and 1,2,4,5-tetra-(chloromethyl)benzene were synthesized by combined chloromethylation and chlorination of xylene.

The methods published for the preparation of the di(chloromethyl)benzenes, namely, chlorination of the xylenes and chloromethylation of benzyl chloride (9, 11, 12), are of limited utility because of low yields due to accompanying side reactions. The purpose of this investigation was to study the conditions of the chloromethylation of benzyl chloride with the aim of improving the yield of the di(chloromethyl)benzenes and to attempt to prepare some heretofore unknown tri- and tetra(chloromethyl)benzenes.

A series of experiments revealed that the chloromethylation of benzyl chloride is influenced by the nature of the solvent, the nature of the condensing agent, and by temperature. Although acetic acid is known to be a satisfactory solvent for the chloromethylation of some aromatic compounds (3, 4, 5, 13), it, as well as other hydroxylated solvents, failed to be effective in the chloromethylation of benzyl chloride. Thus when the reaction was allowed to proceed in different solvents (zinc chloride used as condensing agent at 60 to 70° C.), the following yields of a mixture of the isomeric di(chloromethyl)benzenes were obtained: ethanol—none, butanol—14%, acetic acid—20%, acetic–hydrochloric–phosphoric acid—7% (3), ethylene dichloride—60%, and carbon tetrachloride—60%. Several compounds were examined for their condensing effect on the chloromethylation of benzyl chloride, employing ethylene dichloride as solvent and the fixed temperature. Thionyl, acetyl, calcium, cupric, mercuric, and cadmium chlorides and concentrated sulphuric acid did not catalyze the reaction at all; in each case the starting materials were recovered unchanged except with acetyl and cupric chlorides, where resinous polymers were obtained. A mixture of aluminium chloride and zinc chloride (7) proved a better condensing agent than zinc chloride alone. However, high concentrations of aluminium chloride had to be avoided because of the influence of this compound on the polymerization of benzyl chloride. The chloromethylation of benzyl chloride proceeded only slowly at temperatures below 40° C.; above this, the reaction rate gradually increased, and at higher temperatures side reactions set in, resulting in the formation of

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Contribution from the Research Laboratory, Dominion Rubber Company Limited, Guelph, Ont.

[2] *Chemist.*

diphenylmethane derivatives. Best results were obtained at a temperature of 50°.

Employing the optimum conditions of chloromethylation, a reaction mixture was obtained that was separated by recrystallization and fractional distillation (1) into *p*-di(chloromethyl)benzene (42%), *o*-di(chloromethyl)-benzene (13%), *m*-di(chloromethyl)benzene (3%), and di(*p*-chloromethylphenyl)methane (1%); the remainder could not be separated.

Attempts to introduce a third chloromethyl group into the nucleus of *p*-di(chloromethyl)benzene failed, the starting material being recovered unchanged. 1,2,4-Tri(chloromethyl)benzene was finally prepared by the chlorination (8) of 1,4-dimethyl-2-(chloromethyl)benzene, 2,4-dimethyl-1-(chloromethyl)benzene, or 1,2-dimethyl-4-(chloromethyl)benzene, which were prepared from *p*-, *m*-, and *o*-xylene respectively by chloromethylation (2, 14). 1,2,4,5-Tetra(chloromethyl)benzene was prepared similarly from 1,5-dimethyl-2,4-di(chloromethyl)benzene (2).

Experimental

1,4-Di(chloromethyl)benzene

(a) From Benzyl Chloride

Into a three-necked, three-litre flask fitted with a mechanical stirrer, condenser, and a T-gas-delivery-tube (6, p. 311) was introduced benzyl chloride (200 gm.), trioxymethylene (70 gm.), condensing agent (110 gm.) (fused zinc chloride (105 gm.) to which aluminium chloride (5 gm.) was added with stirring until cool), and ethylene dichloride (400 cc.). The reaction mixture was maintained at 50° C. on a water-bath and stirred vigorously (inefficient stirring resulted in lower yields) for eight hours while dry hydrogen chloride gas was passed in. After standing overnight at room temperature, the reaction mixture was warmed to dissolve the crystals that separated, and more ethylene dichloride was added. The organic layer was separated, washed with water and with a solution of sodium bicarbonate, and dried. The solvent was removed and the residue distilled, yielding unchanged benzyl chloride (5 gm.), a mixture of the xylylene dichlorides, b.p. 100 to 160° C. (10 mm.) (215 gm.), and a residue (36 gm.). Fractional distillation of the residue (36 gm.) and recrystallization of the solid fractions from ether–petroleum-ether yielded di(*p*-chloromethylphenyl)methane (10) (3.8 gm.), m.p. 109 to 110° C.*. Hydrolysis of di(*p*-chloromethylphenyl)methane with boiling 7% aqueous sodium carbonate yielded di(*p*-hydroxy-methylphenyl)methane (10), m.p. 122 to 123° C. The mixture of the xylylene dichlorides (215 gm.) was recrystallized from ethanol, yielding *p*-di(chloromethyl)benzene (117 gm.) (42%), m.p. 98 to 100° C. The filtrate containing the other xylylene dichlorides was taken to dryness and the residue distilled from a Cooke–Bower column (1), yielding *o*-di(chloromethyl)benzene (36 gm.) (13%), from petroleum ether, m.p. 54 to 55° C.; *m*-di(chloromethyl)benzene (8.5 gm.) (3%), from ethanol, m.p. 32 to 34° C.;

**All melting points are corrected.*

and a liquid (35.3 gm.), which in all probability was an inseparable mixture of the xylylene dichlorides. The *m*-di(chloromethyl)benzene on hydrolysis with boiling 7% aqueous sodium carbonate yielded *m*-di(hydroxymethyl) benzene, m.p. 46 to 47° C.

(b) From p-Xylene

A mixture of *p*-xylene (21 gm.), sulphuryl chloride (70 gm.), and benzoyl peroxide (0.3 gm.) was heated under reflux in the sunlight for four hours. The reaction mixture, which solidified on cooling, was washed with water and recrystallized twice from ethanol, yielding white crystals (20 gm.) (58%), m.p. 97 to 99° C.; no depression in melting point when mixed with pure *p*-di(chloromethyl)benzene.

1,2,4-Tri(chloromethyl)benzene

(a) From p-Xylene

A mixture of 1,4-dimethyl-2-(chloromethyl)benzene (108 gm.) prepared by chloromethylation of *p*-xylene (2), sulphuryl chloride (216 gm.), and benzoyl peroxide (1.2 gm.) was heated on a steam-bath for eight hours. The reaction mixture was cooled, washed with water and sodium bicarbonate, and dried. Distillation yielded Fraction 1, b.p. 110 to 160° C. (10 mm.) (54 gm.); Fraction 2, b.p. 160 to 167° C. (10 mm.) (91 gm.); and residue (5 gm.). The lower-boiling fraction (54 gm.) was re-treated with sulphuryl chloride, yielding 40 gm. more of a liquid, b.p. 160 to 167° C. (10 mm.). The combined material, b.p. 160 to 167° C. (10 mm.) (131 gm.) (83%), was fractionally distilled from a Cooke–Bower column, yielding a colourless liquid, b.p. 128° C. (1 mm.), and only small amounts of lower-boiling material and residue. Calc. for $C_9H_9Cl_3$: Cl, 47.7%. Found: Cl, 47.9%. This compound liberated hydrogen chloride on standing in the sunlight.

(b) From m- and o-Xylene

2,4-Dimethyl-1-(chloromethyl)benzene prepared from *m*-xylene (2) and 1,2-dimethyl-4-(chloromethyl)benzene prepared from *o*-xylene (2) by chloromethylation when treated with sulphuryl chloride (see Section (*a*)) each yielded 1,2,4-tri(chloromethyl)benzene as in (*a*). (The tri(chloromethyl)-benzenes obtained from *o*-, *m*- and *p*-xylene on treatment with alcoholic potassium cyanide yielded tricyanomethyl derivatives, each melting singly and on admixture of two at a time at 91 to 92° C.).

(c) From Technical Xylene

A mixture of technical xylene (200 gm.), 40% formaldehyde (200 gm.), and concentrated hydrochloric acid (500 cc.) was heated at 70 to 80° C. and stirred for eight hours while hydrogen chloride gas was passed in. The organic layer was separated, washed with water and sodium bicarbonate, and dried. Distillation yielded Fraction 1, (unchanged xylene) (41 gm.); Fraction 2, b.p. 93 to 97° C. (10 mm.) (140 gm.); Fraction 3, b.p. 103 to 150° C. (10 mm.) (45 gm.) (a mixture of the di(chloromethyl)dimethylbenzenes (2)); and residue (7 gm.).

Fraction 2 (140 gm.) was treated with sulphuryl chloride as in Section (*a*), yielding distillate, b.p. 85 to 140° C. (10 mm.) (115 gm.), and a tar (35 gm.). The distillate on re-treatment with sulphuryl chloride yielded the same tri(chloromethyl)benzene as obtained in (*a*) (92 gm.). (No depression of the melting point of the tri(cyanomethyl) derivative when mixed with that obtained in (*a*)).

1,2,4-Tri(cyanomethyl)benzene

To a boiling solution of potassium cyanide (3 gm.) in water (10 cc.) and ethanol (10 cc.) was added a solution of 1,2,4-tri(chloromethyl)benzene (2 gm.) in ethanol (10 cc.) over a period of 15 min. The reaction mixture was heated under reflux for an additional 15 min., diluted with water, and extracted with benzene (a great deal of resinous material remained unextractable). The benzene extract was taken to dryness and the residue distilled. The distillate (0.5 gm.) soon solidified; white needles from ethanol and from ether, m.p. 91 to 92° C. Calc. for $C_{12}H_9N_3$: C, 73.82; H, 4.65; N, 21.53%. Found: C, 73.88; H, 4.66; N, 21.55%.

1,2,4-Tri(iodomethyl)benzene

To a solution of sodium iodide (9 gm.) in acetone (40 cc.) was added a solution of 1,2,4-tri(chloromethyl)benzene (3.5 gm.) in acetone (10 cc.) and the resulting solution heated under reflux for two hours. The acetone was removed under reduced pressure, the residue dissolved in ether, and the ether solution washed with water and sodium thiosulphate. Removal of the ether yielded a yellow solid (7.0 gm.); light-yellow needles from ethyl methyl ketone and ether, m.p. 93 to 95° C. Calc. for $C_9H_9I_3$: C, 21.69; H, 1.83; I, 76.5%. Found: C, 22.17; H, 2.15; I, 76.8%.

1,2,4-Tri(methoxymethyl)benzene

A solution of 1,2,4-tri(chloromethyl)benzene (4.0 gm.), sodium methylate (6 gm.), and methanol (50 cc.) was heated under reflux for four hours. The sodium chloride was filtered off, water (50 cc.) added to the filtrate, and enough sulphuric acid to make the resulting solution 4 *N*. The solution was then heated under reflux for one hour to hydrolyse any acetal group present, cooled, and extracted with ether. The ether extract was washed with sodium bicarbonate and with sodium bisulphite and dried. Removal of the ether yielded a colourless liquid (3.0 gm.) (80%), b.p. 146° C. (10 mm.). Calc. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.59; OCH_3, 44.3%. Found: C, 68.27; H, 8.50; OCH_3, 44.3%.

1,5-Dimethyl-2,4-di(chloromethyl)benzene

Technical xylene (106 gm.), 40% formaldehyde (200 gm.), concentrated hydrochloric acid (300 cc.), and zinc chloride (10 gm.) were stirred and heated at 90 to 95° C. for 12 hr. while hydrogen chloride gas was passed in. The organic layer was separated, washed with water and sodium bicarbonate, and dried. Distillation yielded Fraction 1, b.p. 60 to 110° C. (10 mm.) (58 gm.); Fraction 2, b.p. 110 to 150° C. (10 mm.) (113 gm.); and residue (5 gm.).

Fraction 2 (113 gm.), which solidified, was recrystallized from ether–petroleum-ether, yielding 1,5-dimethyl-2,4-di(chloromethyl)benzene (2) (56 gm.) (27%), m.p. 96 to 98° C. The isomer, 1,3-dimethyl-2,4-di(chloromethyl)benzene (2), remained in the filtrate.

1,2,4,5-Tetra(chloromethyl)benzene

A mixture of 1,5-dimethyl-2,4-di(chloromethyl)benzene (21 gm.), carbon tetrachloride (40 cc.), sulphuryl chloride (40 gm.), and benzoyl peroxide (0.2 gm.) was heated under reflux for 48 hr.; more benzoyl peroxide (0.02 gm.) was added at intervals of eight hours. The reaction mixture was distilled, and the distillate, b.p. 175 to 200° C. (10 mm.), recrystallized from ethylene dichloride; yield, 9.8 gm. (35%), m.p. 138 to 143° C.; parallelopipeds from ethylene-dichloride–ethanol and from ether, m.p. 151 to 153° C. Calc. for $C_{10}H_{10}Cl_4$: C, 44.12; H, 3.68; Cl, 52.2%. Found: C, 44.25; H, 3.89; Cl, 52.2%.

1,2,4,5-Tetra(methoxymethyl)benzene

1,2,4,5-Tetra(chloromethyl)benzene was treated with sodium methylate in a manner similar to that described above for the preparation of 1,2,4-tri(methoxymethyl)benzene; yield, 90%, white crystals from petroleum ether, m.p. 43 to 44° C. Calc. for $C_{14}H_{22}O_4$: C, 66.10; H, 8.72; OCH_3, 48.8%. Found: C, 66.01; H, 8.88; OCH_3, 48.8%.

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NOTE ON A CONVENIENT LABORATORY PREPARATION OF METHYL ISOCYANATE[1]

By Joseph Colucci[2]

Abstract

The method of Schroeter for the preparation of methyl isocyanate from sodium azide and acetyl chloride has been improved by substitution of acetic anhydride for the acid chloride.

Of the many methods for the preparation of methyl isocyanate on a laboratory scale, that of Schroeter (2) depending on the action of sodium azide and acetyl chloride has been considered most satisfactory. It has been found in these laboratories, however, that, even after several distillations resulting in some loss of product each time, acetyl chloride was still present in the methyl isocyanate.

To obtain pure methyl isocyanate it was thought that the use of acetic anhydride might be advisable. The boiling point of acetic anhydride is much higher than that of methyl isocyanate and, therefore, the separation of the two by fractional distillation should be easily effected.

It has now been found that the action of acetic anhydride on sodium azide was more satisfactory than that of acetyl chloride and one fractional distillation was sufficient to yield pure methyl isocyanate.

Experimental

Commercial grade acetic anhydride was distilled through a 10-in. column, and the fraction distilling at a constant temperature was used.

Sodium azide (14.5 gm.) and acetic anhydride (20 gm.) was added to dry isoamyl ether (100 cc.) in a 250 cc. flask with ground-glass joint; the flask was set up in an empty water-bath and fitted with a mechanical stirrer and ground-glass condenser. The receiver was immersed in an acetone–dry-ice bath and the side-arm of the adapter joining the condenser to the receiver was fitted with a glass tube leading into a wash bottle partly immersed in a cold-bath.

Water (70° C.) was then added to the bath around the reaction flask and heated, so that the temperature reached 95° C. in 15 min. An abundant evolution of nitrogen resulted by this time. The bath temperature was kept constant for 15 min., after which it was raised to 100° C. in five minutes. This temperature was maintained for 15 min. Then the bath was removed and the flask cautiously heated with a bare flame, care being taken that a steady evolution of gas took place.

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[2] *Laboratory Assistant.*

When the evolution of gas ceased, heating was stopped and the receiver and wash-bottle were removed from the bath. A small amount of methyl isocyanate that had collected in the wash-bottle was added to the main portion, which was distilled through a 6-in. column packed with glass helices. The receiver was again immersed in acetone–dry-ice. Methyl isocyanate boiled at 36 to 39° C.

Several runs were made using an ice–salt bath but this provided insufficient cooling and the yields were low (45 to 65%). When an acetone–dry-ice bath was employed, the yields of methyl isocyanate averaged 78%.

To ascertain the identity of the methyl isocyanate a small quantity was reacted with *p*-toluidine as described by Boehmer (1), and an excellent yield (96.6%) of α-(4-methylphenyl)-α'-methylurea was obtained which, without recrystallization, melted at 177° C. (corr.). (Boehmer gives m.p. 178° C.)

References

1. Boehmer, J. W. Rec. trav. chim. 55 : 379-391. 1936.
2. Schroeter, G. Ber. 42 : 3356-3362. 1909.

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